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| 09/786,055 | 03/01/2001 | Christian Belmant | BE 8992 | 6944 |

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| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 6 |

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/786,055 | Belmant |
| **Examiner** | **Art Unit** |
| Richard Schnizer | 1635 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Sep 27, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above, claim(s) *8* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7 and 9-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Mar 1, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicant's amendment received 9/2702 was entered as Paper No. 5

The election with traverse of group I, drawn to claims 1-7 and 9-28, and the species of phosphoepoxides is acknowledged. Traversal of the restriction requirement is on the grounds that no lack of unity was found in the international phase of the corresponding PCT application. Applicant asserts that the Office cannot contend that there is an undue search burden. This is unpersuasive because search burden is not a consideration under PCT Rules 13.1 and 13.2 regarding unity of invention. Rather the presence or absence of a special technical feature is assessed. Furthermore, the Office is not bound by the findings in the International Phase of the PCT. Applicant further argues that no evidence was provided that the claims do not relate to a single inventive concept. This is unpersuasive because the Office relied upon Muehlbacher et al (1988) as evidence. This reference is disclosed in Applicant's information disclosure statement, so the Office assumes that Applicant is in possession of the evidence. Furthermore, Applicant admits at page 5, lines 9-24 of the specification that Muehlbacher teaches a compound with the structural characteristics required by claim 1. The recited intended therapeutic use of the compound cannot be part of the special technical feature because it is not shared by all of the claims. See e.g. claim 3. For these reasons the Muehlbacher reference anticipates claim 1 and destroys unity of invention under PCT Rules 13.1 and 13.2. The requirement is still deemed proper and is therefore made FINAL. In order to obtain consideration of non-elected claim 8, Applicant should clarify the structure of the claimed compound. In view of the speciication at

page 7, lines 7 and 8, the notation "PP" recited in claim 8 could be considered to refer to a pyrophosphate group. If this is the case, then Applicant should amend claim 8 to clarify the structure of the claimed compound, consistent with the format used, for example, in claims 1-5.

The species election requirement is withdrawn because a search of the prior art showed all species of claims 18 and 25-28 to be novel and non-obvious.

As noted below under 35 USC 112, second paragraph rejections claim 7 is indefinite because it recites "R2" without antecedent basis. As such it is unclear what is the structure of the species set forth in claim 7. For the purpose of examination in this Office Action, "R2" is considered to be appended to the terminal phosphate shown in formula (1) of claim 1.

***Claim Objections***

Claims 12-16, and 24 are objected to because of the following informalities.

Claims 12-16 are objected to because they are ungrammatical. The article "A" should be inserted as the first word in each of these claims.

Claim 12 is objected to because the first instance of "Cat" lacks a "+" sign.

Claim 13 is objected to because it does not end in a period.

Claim 24 is objected to because it is improperly multiply dependent fo referrring to two sets of claims for different features. See MPEP 608.01(n)(B)(3). Claim 24 is drawn to the method of claim 20, but also recites the compositions of claims 1-11.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 9, 11, 16, 17, and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the claimed phosphoepoxides for the purpose of activating Tγ9δ2, does not reasonably provide enablement for the use of these compositions in therapy, prevention, or curative treatent of any pathological condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors.

*Nature of the invention.*

The invention is drawn to phosphoepoxide compositions and methods of making the compositions. The phosphoepoxides activate Tγ9δ2 cells which are known to have antitumoral and antiviral effects in vivo. The rejected claims require that the compositions must be useful for therapy. The specfication teaches that the claimed compositions can be used to activate Tγ9δ2 cells ex vivo. Use of ex vivo-activated T-cells for therapy is known as adoptive immunotherapy.

*Breadth of the claims*

Claims 1, 2, 6, 7, 9, 11, 16, and 17 are drawn to genuses of phosphoepoxide compositions, and explicitly recite an intended use in any therapy. Claims 21-24 are drawn to processes for the production of therapeutic compositions intended for preventive or curative treatment of any pathological condition that produces cells sensitive to Tγ9δ2 lymphocytes.

*State of the prior art*

Yamaguchi et al (J. Immunol. Met. 205(1): 19-28, 6/23/97) taught that gamma delta T cells make up no more than 10% of peripheral blood mononuclear cells, but appear to play an important role in host defense against tumor growth. In order to evaluate their functional acitivity against tumors, large quantities of cells are required. Yamaguchi teaches a method of producing large quantities of gamma delta T cells by isolating them inducing TCR/CD3-mediated signal transduction by contacting the cells with an anti-CD3 antibody and IL-2. Yamaguchi notes that this method may make it possible to produce sufficient numbers of gamma delta T cells for clinical trials of anti-tumor adoptive immunotherapy. See abstract. Thus it was recognized in the art at the time of the invention that obtaining a sufficient number of gamma delta T cells was an obstacle to adoptive immunotherapeutic methods relying on these cells. Although Yamaguchi taught a potential solution to this problem, it was clear that those of skill in the art would not be convinced that the teachings of Yamaguchi were suffcient to solve the problem. For example, Janssen et al (J. Immunol. 146(1): 35-39, 1/1/91) taught that stimulation of gamma delta cells with anti-CD3 antibody and IL-2 led ultimately to cell death through apoptosis, thus calling into question the usefulness of this method for expanding gamma delta cells to the numbers needed for therapeutic

purposes. Indeed Lopez et al (Blood 96(12): 3827-3837, 12/1/2000) taught that the exploitation of gamma delta T cells for therapeutic ends remained largely unrealized because of the extreme difficulty in obtaining sufficient quantities of these cells. Lopez noted that while treatment of gamma delta T cells with anti-CD3 or anti-TCR antibodies is an attractive means of expanding these cells, this method results in apoptosis, thereby presenting a serious obstacle to developing approches to incorporate gamma delta T cells into any form of adoptive immunotherapy. See page 3827, column 2, lines 2-18. Lopez concluded, "[w]hether γδ-T cells have therapeutically exploitable biologic properties such as antiviral, antitumor, or hematopoitic stem cell graft-facilitating effects, remians to be determined." See page 3836, column 2, lines 5-8. Lopez indicates that amounts of cells far in excess of $10^9$ would be needed for therapeutic purposes. See page 3836, lines 7-17.

A search of the prior art revealed no instances of complete disease prevention or cure through the use of Tγ9δ2 cell adoptive immunotherapy.

*Unpredictability in the art*

The teachings of Janssen (1991) and Lopez (2000) above show that at the time of the invention, the art of adoptive immunotherapy using Tγ9δ2 cells was highly unpredictable, essentially because of the technical difficulty in obtaining sufficient numbers of apoptosis-resistant cells. Furthermore, even if a sufficient number of cells could be obtained, it was not predictable that these cells would be useful for any therapeutic method. See page 3836, column 2, lines 5-8.

*Guidance and exemplification in the specification*

The specification teaches how to make phosphoepoxide compounds and demonstrates that they can be used to stimulate proliferation of Tγ9δ2 cells in the presence of IL2. See e.g. pages 25-33 of the specification. The specification fails to teach the production of quantities of Tγ9δ2 cells approaching $10^9$, and fails to provide any information as to the mechanism of Tγ9δ2 cell proliferation, or any apoptotic effects of phosphoepoxide-mediated mitogenesis.

*Amount of experimentation required*

Due to the unpredictable nature of the art of Tγ9δ2 cell adoptive immunotherapy, the recognition in the art that larger numbers of Tγ9δ2 cells were required for therapy than could be produced by existing methods, the failure of the specification to teach how to produce sufficient numbers of cells for therapeutic purposes , and whether or not these cells are subject to apoptosis, particularly in view of their treatment with IL2, one of skill in the art would have to perform undue experimentation to use the claimed compositions for therapeutic purposes as required by the claims.

This rejection can be overcome by removing requirements for therapy, disease prevention, and disease curing from the claims. It is noted that independent claim 3 was not included in this rejection, although. its dependent claim, claim 9, was included. Claim 3 is a composition claim in which al least one non-therapeutic use is considered to be enabled. A composition claim need have only one enabled use to satisfiy the requirements of l 12, first paragraph. However, claim 9 requires that the composition must be enabled for a therapeutic use. This use is not considered to be enabled for the reasons set forth above, so claim 9 is appropriately rejected, even though claim

3 is not rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-9, 11-15, 18, 19, and 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-5, 8, 9, 15, 18 and 19 are indefinite because it is unclear how the term "novel" limits these claims. Whether or not a particular composition is novel depends on the time at which the composition is considered. At the time of the invention a particular composition may be novel, however, after the composition is disclosed it is no longer novel and the term loses its meaning, rendering the claim indefinite.

Claim 5 is indefinite because it is not clear what is intended by "the group comprising". In this context, the term "comprising" is considered to be open language, and it is not clear what compounds, if any, Applicant wishes to exclude from the group. Thus one of skill in the art cannot know the metes and bounds of the claim. This rejection can be overcome by substituting the word "consisting" for the word "comprising".

Claim 5 is also indefinite because it recites "the triphosphate group" without antecedent basis.

Claims 6 and 7 are indefinite because it is unclear how "nucleic acids (DNA, RNA)" is intended to limit the claims. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. In this case, the parenthetical inclusion of "DNA, RNA" after "nucleic acids" is considered to be equivalent to "such as". It is not clear if the claim is intended to exclude, for example hybrid molecules comprising both DNA and RNA or peptide nucleic acids. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claims 6 and 7 are also indefinite because it is unclear what is the distinction between "simple" and "complex" lipids. The specification fails to define these terms, and it is unclear where is the threshold between simple and complex.

Claim 7 is indefinite because it recites "R2" without antecedent basis.

Claim 7 is indefinite because it recites "the formula (I)" without antecedent basis. The parent claim refers to the formula "(1)", not "(I)".

Claim 11 is indefinite because it is unclear how the phrase "in particular an immunostimulant therapeuutic composition" is intended to further limit the claim. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. In this case, the phrase "in particular" is considered to be equivalent to "such as". Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claims 12-14 are indefinite because it recites "the formula", in line 14 of claim 12, without proper antecedent basis.

Claims 12-14 are also indefinite because they are ungrammatical. There is no connection between the purpose set forth in the preamble and the recited method steps in claim 12. Inclusion of the the word "and" immediately before the phrase "the intermediate compound" is suggested.

Claim 13 is indefinite because it recites "the halogen X2" without antecedent basis.

Claim 19 is indefinite because it recites "the medium into which it is to be administered" without antecedent basis.

Claims 20-24 are indefinite because although claims 20-23 are drawn to methods, they recite no method steps. Claim 24 is included in the rejection because although it recites a method step, it also requires performance of themethod of claim 20, which has no method steps.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 10, 16, 17, 20, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Muehlbacher et al (Biochemistry 27:7315-7328, 1988).

Muehlbacher teaches a diphosphoepoxide according to formula (2) of claim 2. Sce attached search result. This is admitted in the specification at page 5, lin.es 17-24. Muehlbacher also teaches methods of making the compound. See "Synthesis of lnhibitors" at pages 7316-7321, particularly first and second full paragraphs in column 2 of page 7320. Although the rejected

claims recite or imply an intended use of therapy, any activity of the compound is considered to be irdlerent in its strtucture. Because Muehlbacher teaches the structure, Muehlbacher anticipates the claims.

***Summary***

Claims 12-16 and 24 are objected to over informalities.

Claims 1, 2, 6, 7, 9, 11, 16, 17, and 21-28 are not adequately enabled.

Claims 3-9, 11-15, 18, 19, and 20-24 are indefinite.

Claims 1, 2, 10, 16, 17, 20, 22, and 23 are anticiapted.

Claims 3-7, 9, 11-15, 18, 19, 21, and 24-28 are free of the prior art of record.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
12/16/02